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Inventors: **Huber et al.**
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REMARKS

Claims 51-76, 79-81, 84-92, 95 and 97 are pending in this application. Claims 51-76, 79-81, 84-92, 95 and 97 have been rejected. No new matter has been added by this amendment. Reconsideration is respectfully requested in light of the following remarks and amendments.

I. Rejection under 35 U.S.C. 102(a)/103(a)

A. Gusev as Primary Reference

Claims 51-76, 79-81, 84-92, 95 and 97 stand rejected under 35 U.S.C. 102(a) as anticipated by or in the alternative under 35 U.S.C. 103(a) as obvious over Gusev et al. (1999) *J. Chromatography*, pg. 273-290. The claims are suggested to read on Gusev et al. and it would have been obvious to optimize the elements of Gusev et al. to enhance separation.

Claims 57-58 and 66 also stand rejected under 35 U.S.C. 103(a) as being unpatentable over Gusev et al. in view of Peters (U.S. Patent No. 5,929,214) for reasons of record. The Examiner acknowledges that Gusev et al. fail to teach channels sufficiently large to allow convective flow; however, Peters is said to disclose large channels allowing for convective flow and high flow rates through a monolith.

Claim 91 stands rejected under 35 USC 103(a) as being unpatentable over Gusev in view of Girot (US Patent 6,045,697). It is acknowledged that Gusev et al. do not recite the use of a tetrahydrofuran porogen; however, Girot is said to disclose that tetrahydrofuran is a suitable porogen.

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Claim 95 remains rejected under 35 USC 103(a) as being unpatentable over Gusev, in view of either Huber ((1998) *Anal. Chem.* 70:5288-95) or Griffey ((1997) *J. Mass. Spec.* 32:305-13). It is suggested that the claim differs from Gusev in reciting use of a mass spectrometer. It is suggested that Huber discloses electrospray mass spectrometry and Griffey discloses that electrospray mass spectrometry is a gentle sensitive method of analysis.

The Examiner suggests that Applicants' affidavit submitted with the response dated March 25, 2004 and Applicants' response dated October 28, 2005 fail to establish Applicants' reduction to practice of the instant invention. It is suggested that the declaration itself does not state that the work was performed in a U.S., a NAFTA country or a WTO country. It is further suggested that the declaration does not indicate that the monolith was in a fused silica tube having a diameter in the range of 1 to 1000 micrometers, the chromatographic surfaces were non-polar, or that the matrix was underivatived and that the Polymicro Technology Literature specifying these features is not of record. Applicants respectfully disagree and traverse these rejections.

Gusev fails to describe the present invention as this reference does not teach the use of channels sufficiently large to allow convection flow, nor does this reference teach separation of polynucleotides. Moreover, Gusev is not a proper prior art reference under 35 U.S.C. 102(a), because prior to the effective date of this reference, Applicants had reduced to practice the present invention. Applicants submit herewith a Rule 131 Declaration by Applicant, Christian Huber, which indicates that

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prior to the effective date of Gusev, Applicants had carried out the synthesis of PS/DVB monolith using decanol and tetrahydrofuran as porogens and successfully separated oligonucleotides using this monolith. As disclosed at page 17 (lines 30-32) and page 22 (lines 25-27) of the instant specification, poly(styrene-divinylbenzene), also referred to as PS-DVB, is underivatized and has a nonpolar chromatographic surface. Accordingly, the laboratory notebook pages submitted with the Declaration demonstrate that Applicants had diligently reduced to practice the use of monoliths having an underivatized matrix with nonpolar chromatographic surfaces prior to the effective date of Gusev et al., i.e., September 3, 1999. Further, page 28 (lines 25-27) of the specification indicates that polyimide-coated fused silica capillary tubing is available from Polymicro Technologies (Phoenix, AZ). In this regard, line 7 of the last page of the experimental results provided in the Declaration indicates that a 6 cm TSP025375 column was employed in February 1999 for chromatographically separating dT₁₂ to dT₁₈ oligonucleotides in monolith (see page header and graphs). Polymicro Technologies product literature indicates that TSP025375 is a fused silica tube having an inner diameter of 25 µm and outer diameter of 363 µm. See product literature enclosed herewith. As such, Applicants had reduced to practice the use of a polymeric monolith in a fused silica tube having an inner diameter in the range of 1 micrometer to 1000 micrometer prior to the effective date of the Gusev reference.

Accordingly, in addition to failing to teach the instant invention, Gusev et al. is not a proper prior art reference under 35 U.S.C. 102(a), as the present invention was invented prior to the publication of Gusev et al., as evidenced by Applicants'

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Declaration. Because the secondary references of Peters, Huber, Griffey and Girot fail to teach or suggest all of the claim limitations of the present invention, the instant invention is neither anticipated nor obvious in view of Gusev et al., Peters, Huber, Griffey and Girot. Reconsideration and withdrawal of this rejection is therefore respectfully requested.

B. Frechet or Hatch as Primary Reference

Claims 51-66, 71, 73-76, 79-81, 84-85 and 95 stand rejected under 35 USC 103(a) as being unpatentable over either Frechet U.S. Patent No. 5,334,310) or Hatch (U.S. Patent No. 6,238,565) in view of Peters ((1997) *Anal. Chem.* 69:3646-49), Huang ((1997) *J. Chromatography* 788:155-64) and Tomer ((1994) *Mass. Spec. Rev.* 13:431-57) for the reasons of record.

Claims 67-70 and 72 stand rejected under 35 U.S.C. 103 (a) as being unpatentable over either Frechet or Hatch in view of Peters and Huang for the reasons of record.

Claims 86-92 and 97 stand rejected under 35 U.S.C. 103 (a) as being unpatentable over either Frechet or Hatch in view of Peters and Tomer for the reasons of record.

Claims 57-58 and 66 stand rejected under 35 USC as being unpatentable over either Frechet or Hatch in view of Peters, Huang and Tomer as applied to claims 51-66, 71, 73-76, 79-85 and 95 above, and further in view of Peters (Patent '214) for the reasons of record.

Claim 91 stands rejected under 35 U.S.C. 103(a) as being unpatentable over either Frechet or Hatch in view of Peters and

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Tomer as applied to claims 86-92 and 97 above and further in view of Girot for the reasons of record.

Claim 95 stands rejected under 35 U.S.C. 103(a) as being unpatentable over either Frechet or Hatch in view of Peters, Huang and Tomer as applied to claims 51-66, 71, 73-76, 79-85 and 95 above, and further in view of Huber or Griffey for the reasons of record.

Applicants respectfully traverse these rejections.

At the outset, as indicated above, Applicants had reduced to practice the use of a polymeric monolith in a fused silica tube having an inner diameter in the range of 1 micrometer to 1000 micrometer prior to the effective date of Hatch, September 16, 1998. Therefore, Hatch cannot be considered to be a valid prior art reference.

Further, MPEP 2142 indicates that to establish a *prima facie* case of obviousness three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure.

A *prima facie* case of obviousness has not been met. At the outset, the referenced teachings are absent any motivation to modify or combine the teachings therein. The Patent Office "cannot

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use hindsight reconstruction to pick and choose among isolated disclosure in the prior art to deprecate the claimed invention." *In re Fine*, 837 F.2d 1071, 1075, 5 USPQ2d 1780, 1783 (Fed. Cir. 1988). Rather, in making a rejection under 35 U.S.C. 103(a), the Patent Office must show a teaching or motivation to combine the cited prior art references. See *Dembiczak*, 1783 F.3d at 999, 50 USPQ2d at 1617. "Combining prior art references without evidence for such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability--the essence of hindsight." *Id.* Therefore, "[w]hen determining the patentability of a claimed invention which combines two known elements, 'the question is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination.'" *In re Beattie*, 974 F.2d 1309, 1311-12, 24 USPQ2d 1040, 1042 (Fed. Cir. 1992) (quoting *Lindemann*, 730 F.2d at 1462, 221 USPQ at 488).

In this regard, the Examiner has used the rejected claims as a blueprint for reconstructing the elements of the claimed invention on the basis that Peters "discloses that the use of a fused silica column eliminates the need for initial chemical modification of the walls of the capillary." However, there must be evidence that "a skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art reference for combination in the manner claimed." *In re Rouffet*, 149 F.3d at 1357, 47 USPQ2d at 1456. The present invention is drawn to monoliths comprising an underivatized poly(styrene-divinylbenzene) matrix for separating a mixture of polynucleotides. As is well-known to the skilled

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artisan, the nature of the molecules to be separated significantly influences the medium selected for separation. In this regard, while the primary references of Hatch, Frechet, and Huang teach column matrices composed of poly(styrene-divinylbenzene) for separation of proteins or nucleic acids, Peters teaches rigid monoliths composed of ethylene dimethacrylate, butyl methacrylate, and 2-acrylamido-2-methyl-1-propanesulfonic acid in the separation of benzene derivatives. Based on the content of these disclosures there would simply be no rationale for the skilled artisan to look to Peters to identify a fused silica tube for use with the poly(styrene-divinylbenzene) matrix of Hatch or Frechet to separate polynucleotides, because the separation medium and nature of the molecules separated by Peters are significantly different from that of Hatch or Frechet.

In addition to the absence of motivation, there is no teaching or suggestion to combine the referenced teachings. In particular, while Hatch and Frechet teach column matrices composed of poly(styrene-divinylbenzene), nowhere in the teachings of Frechet or Hatch do Applicants find reference to a fused silica tube or covalent attachment of the matrix to the inner wall of the tube. Moreover, while Peters teaches a fused-silica capillary tube containing rigid monoliths composed of ethylene dimethacrylate, butyl methacrylate, and 2-acrylamido-2-methyl-1-propanesulfonic acid, this reference fails to teach or suggest a poly(styrene-divinylbenzene) matrix or covalent attachment of the matrix to the inner wall of the tube. Accordingly, these references fail to provide any teaching or suggestion in combining the teachings therein to make the claimed invention.

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In so far as Tomer teaches column dimensions, Peters (Patent '214) teaches flow rates, Girot teaches tetrahydrofuran as a porogen, and Huber or Griffey teach EMS, these references fail to overcome the deficiencies in Frechet or Hatch in view of Huang and Peters. Thus, these references cannot be held to make obvious the present invention. Because all three basic criteria for establishing a *prima facie* case of obviousness have not been met in this case, it is respectfully requested that the rejections under 35 U.S.C. 103(a) be reconsidered and withdrawn.

II. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,



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